Claims

What is claimed is:

1. A pharmaceutical formulation comprising a CD4-IgG2 chimeric heterotetramer and a histidine buffer, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 15-162 mg/ml and said formulation has a pH of between about 5.5-6.5.
2. The formulation according to claim 1, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 15-30 mg/ml.
3. The formulation according to claim 2, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 25 mg/ml.
4. The formulation according to claim 1, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 100-162 mg/ml.
5. The formulation according to claim 4, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 100 mg/ml.
6. The formulation according to claim 4, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 140-150 mg/ml.
7. The formulation according to claim 1, wherein the formulation has a pH of about 6.0.
8. The formulation according to claim 1, wherein the histidine buffer is present in said formulation at a concentration of between about 5-50 mM.
9. The formulation according to claim 8, wherein the histidine buffer is present in said formulation at a concentration of about 20 mM.
10. The formulation according to claim 1, wherein the formulation is stable at a temperature of 8°C or less for at least two months.

11. The formulation according to claim 1, wherein the formulation is stable at a temperature of 8°C or less for at least six months.

12. The formulation according to claim 1, wherein the formulation is stable at a temperature of 8°C or less for at least twelve months.

13. The formulation according to claim 1, wherein the formulation is stable at a temperature of 8°C or less for at least twenty-four months.

14. The formulation according to claim 1, wherein the formulation is stable at a temperature of -90°C for at least twenty-four months.

15. The formulation according to claim 1, wherein the formulation is lyophilized and wherein the lyophilized formulation is stable at an ambient temperature for at least twenty-four months.

16. The formulation according to claim 1, wherein the formulation is stable following at least one freezing and thawing of the formulation.

17. In combination, the formulation according to claim 1 and a sealable container containing said formulation.

18. In combination, the formulation according to claim 1 and a vial or ampoule containing said formulation, said vial or ampoule having a septum.

19. In combination, the formulation according to claim 1 and a sealable bottle containing said formulation.

20. In combination, the formulation according to claim 1 and a syringe containing said formulation.

21. In combination, the formulation according to claim 1 and an infusion bag containing said formulation.

22. The formulation according to claim 1, wherein the formulation is suitable for parenteral administration.

23. The formulation according to claim 22, wherein the parenteral administration is performed intravenously, subcutaneously or intramuscularly.

24. The formulation according to claim 1, wherein said formulation is substantially free of CD4-IgG2 chimeric heterotetramer aggregates and degradation products.

25. The formulation according to claim 1, wherein the CD4-IgG2 chimeric heterotetramer is in at least 96% monomeric form.

26. The formulation according to claim 1, wherein the CD4-IgG2 chimeric heterotetramer is in at least 97% monomeric form.

27. The formulation according to claim 1, wherein the CD4-IgG2 chimeric heterotetramer is in at least 98% monomeric form.

28. The formulation according to claim 1, wherein the CD4-IgG2 chimeric heterotetramer is in at least 99% monomeric form.

29. A pharmaceutical formulation comprising a CD4-IgG2 chimeric heterotetramer, a histidine buffer and an amino acid stabilizing agent, wherein the heterotetramer is present in said formulation at a concentration of between about 15-162 mg/ml and said formulation has a pH of between about 5.5 and 6.5.

30. The formulation according to claim 29, wherein the chimeric heterotetramer is present in said composition at a concentration of between about 15-30 mg/ml.

31. The formulation according to claim 30, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 25 mg/ml.

32. The formulation according to claim 29, wherein the chimeric heterotetramer is present in said composition at a concentration of between about 100-162 mg/ml.

33. The formulation according to claim 32, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 100 mg/ml.

34. The formulation according to claim 32, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 140-150 mg/ml.

35. The formulation according to claim 29, wherein the formulation has a pH of about 6.0.

36. The formulation according to claim 29, wherein the histidine buffer is present in said formulation at a concentration of between about 5-50 mM.

37. The formulation according to claim 36, wherein the histidine buffer is present in said formulation at a concentration of about 20 mM.

38. The formulation according to claim 29, wherein the amino acid stabilizing agent is selected from the group consisting of alanine, glycine, proline and glycylglycine.

39. The formulation according to claim 38, wherein the amino acid stabilizing agent is present in said formulation at a concentration of between about 25-150 mM.

40. The formulation according to claim 38, wherein the amino acid stabilizing agent is glycine.

41. The formulation according to claim 40, wherein the glycine is present in said formulation at a concentration of about 50 mM.

42. A pharmaceutical formulation comprising a CD4-IgG2 chimeric heterotetramer, a histidine buffer and a lyoprotectant, wherein the heterotetramer is present in said formulation at a concentration of between about 15-162 mg/ml and said formulation has a pH of between about 5.5 and 6.5.

43. The formulation according to claim 42, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 15-30 mg/ml.

44. The formulation according to claim 43, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 25 mg/ml.

45. The formulation according to claim 42, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 100-162 mg/ml.

46. The formulation according to claim 45, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 100 mg/ml.

47. The formulation according to claim 45, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 140-150 mg/ml.

48. The formulation according to claim 42, wherein the formulation has a pH of about 6.0

49. The formulation according to claim 42, wherein the formulation further comprises an amino acid stabilizing agent selected from the group consisting of alanine, glycine, proline and glycylglycine.

50. The formulation according to claim 49, wherein the amino acid stabilizing agent is present in said formulation at a concentration of between about 25-150 mM.

51. The formulation according to claim 50, wherein the amino acid stabilizing agent is glycine and the glycine is present in said formulation at a concentration of about 50 mM.

52. The formulation according to claim 42, wherein the histidine buffer is present in said formulation at a concentration of between about 5-50 mM.

53. The formulation according to claim 52, wherein the histidine buffer is present in said formulation at a concentration of about 20 mM.

54. The formulation according to claim 42, wherein the composition is lyophilized.

55. The formulation according to claim 42, wherein the lyoprotectant is sucrose or trehalose.

56. The formulation according to claim 55, wherein the lyoprotectant is trehalose.

57. The formulation according to claim 55, wherein the lyoprotectant is present in said formulation at a concentration of between about 1.5-3.0%.

58. The formulation according to claim 57, wherein the lyoprotectant is trehalose and wherein the trehalose is

present in said formulation at a concentration of about 1.8%.

59. A pharmaceutical formulation comprising a CD4-IgG2 chimeric heterotetramer, a histidine buffer and a nonionic detergent, wherein the heterotetramer is present in said formulation at a concentration of between about 15-162 mg/ml and said formulation has a pH of between about 5.5-6.5.

60. The formulation according to claim 59, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 15-30 mg/ml.

61. The formulation according to claim 60, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 25 mg/ml.

62. The formulation according to claim 59, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 100-162 mg/ml.

63. The formulation according to claim 62, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 100 mg/ml.

64. The formulation according to claim 62, wherein the heterotetramer is present in said formulation at a concentration of between about 140-150 mg/ml.

65. The formulation according to claim 59, wherein the formulation has a pH of about 6.0.

66. The formulation according to claim 59, wherein the formulation further comprises an amino acid stabilizing agent selected from the group consisting of alanine, glycine, proline and glycylglycine.

67. The formulation according to claim 66, wherein the amino acid stabilizing agent is present in said formulation at a concentration of between about 25-150 mM.

68. The formulation according to claim 67, wherein the amino acid stabilizing agent is glycine and the glycine is present in said formulation at a concentration of about 50 mM.

69. The formulation according to claim 59, wherein said formulation further comprises a lyoprotectant.

70. The formulation according to claim 69, wherein the lyoprotectant is sucrose or trehalose.

71. The formulation according to claim 70, wherein the lyoprotectant is trehalose.

72. The formulation according to claim 70, wherein the lyoprotectant is present in said formulation at a concentration of between about 1.5-3%.

73. The formulation according to claim 72, wherein the lyoprotectant is trehalose and wherein the trehalose is present in said formulation at a concentration of about 1.8%.

74. The formulation according to claim 59, wherein the nonionic detergent comprises a polysorbate composition.

75. The formulation according to claim 74, wherein the polysorbate composition is polyoxyethylenesorbitan monooleate.

76. The formulation according to claim 59, wherein the nonionic detergent is present in said formulation at a concentration of between about 0.02-0.05%

77. The formulation according to claim 76, wherein the nonionic detergent is present in said formulation at a concentration of about 0.05%.

78. The formulation according to claim 59, wherein the histidine buffer is present in said formulation at a concentration of between about 5-50 mM.

79. The formulation according to claim 78, wherein the histidine buffer is present in said formulation at a concentration of about 20 mM.

80. A pharmaceutical formulation comprising a CD4-IgG2 chimeric heterotetramer, a histidine buffer and at least one osmolality adjusting agent, wherein the heterotetramer is present in said formulation at a concentration of between about 15-162 mg/ml and said formulation has a pH of between about 5.5-6.5.

81. The formulation according to claim 80, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 15-30 mg/ml.

82. The formulation according to claim 81, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 100-162 mg/ml.

83. The formulation according to claim 82, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 100 mg/ml.

84. The formulation according to claim 82, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 140-150 mg/ml.

85. The formulation according to claim 80, wherein said formulation has a pH of about 6.0.

86. The formulation according to claim 80, wherein the formulation further comprises an amino acid stabilizing agent selected from the group consisting of alanine, glycine, proline and glycylglycine.

87. The formulation according to claim 86, wherein the amino acid stabilizing agent is present in said formulation at a concentration of between about 25-150 mM.

88. The formulation according to claim 87, wherein the amino acid stabilizing agent is glycine and the glycine is present in said formulation at a concentration of about 50 mM.

89. The formulation according to claim 80, wherein the formulation further comprises a lyoprotectant.

90. The formulation according to claim 89, wherein the lyoprotectant is sucrose or trehalose.

91. The formulation according to claim 90, wherein the lyoprotectant is trehalose.

92. The formulation according to claim 90, wherein the lyoprotectant is present in said formulation at a concentration of between about 1.5-3%.

93. The formulation according to claim 92, wherein the lyoprotectant is trehalose and wherein the trehalose is

present in said formulation at a concentration of about 1.8%.

94. The formulation according to claim 80, wherein the at least one osmolality adjusting agent is selected from the group consisting of maltose, trehalose and glycine.

95. The formulation according to claim 94, wherein the at least one osmolality adjusting agent is present in said formulation in a concentration of between about 4-10%

96. The formulation according to claim 95, wherein the at least one osmolality adjusting agent is maltose and the maltose is present in said formulation at a concentration of between about 6-7%.

97. The formulation according to claim 80, wherein the at least one osmolality adjusting agent is present in said formulation in a concentration to provide an osmolality of about 216-320 mOsm/kg.

98. The formulation according to claim 80, wherein the at least one osmolality adjusting agent is present in said formulation at a concentration to provide an osmolality of about 220-300 mOsm/kg.

99. The formulation according to claim 80, wherein the at least one osmolality adjusting agent is present in said formulation at a concentration to provide an osmolality of about 280 mOsm/kg.

100. A pharmaceutical formulation comprising a CD4-IgG2 chimeric heterotetramer, a histidine buffer, an amino acid stabilizing agent, a lyoprotectant and at least one osmolality adjusting agent, wherein the heterotetramer is present in said formulation at a concentration of between about 15-162 mg/ml, wherein the buffer is present in said formulation at a concentration of between about 5-50 mM, wherein the amino acid stabilizing agent is selected from the group consisting of alanine, glycine, proline and glycylglycine and is present in said formulation at a concentration of between about 25-150 mM, wherein the lyoprotectant is sucrose or trehalose and is present in the formulation at a concentration of between about 1.5-

3%, wherein the at least one osmolality adjusting agent is selected from the group consisting of maltose, trehalose and glycine and is present in the formulation at a concentration of between about 4-10% and wherein said formulation has a pH of between about 5.5 and 6.5.

101. The formulation according to claim 100, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 15-30 mg/ml.

102. The formulation according to claim 101, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 25 mg/ml.

103. The formulation according to claim 100, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 100-162 mg/ml.

104. The formulation according to claim 103, wherein the chimeric heterotetramer is present in said formulation at a concentration of about 100 mg/ml.

105. The formulation according to claim 103, wherein the chimeric heterotetramer is present in said formulation at a concentration of between about 140-150 mg/ml.

106. The formulation according to claim 100, wherein the formulation further comprises a nonionic detergent.

107. The formulation according to claim 106, wherein the nonionic detergent comprises a polysorbate composition.

108. The formulation according to claim 100, wherein the at least one osmolality adjusting agent is present in said formulation at a concentration to provide an osmolality of about 216-320 mOsm/kg.

109. The formulation according to claim 100, wherein the at least one osmolality adjusting agent is present in said formulation at a concentration to provide an osmolality of about 220-300 mOsm/kg.

110. The formulation according to claim 100, wherein the at least one osmolality adjusting agent is present in said formulation at a concentration to provide an osmolality of about 280 mOsm/kg.

111. A method of inhibiting infection of a CD4+ cell by a human immunodeficiency virus, which method comprises contacting the human immunodeficiency virus with an amount of the formulation according to any one of claims 1, 29, 42, 59, 80 and 100 effective to form a complex with such human immunodeficiency virus which is in the presence of the CD4+ cell, so as to thereby inhibit infection of the CD4+ cell by the virus.

112. A method of preventing CD4+ cells of a subject from becoming infected with human immunodeficiency virus, which method comprises administering to the subject an amount of the formulation according to any one of claims 1, 29, 42, 59, 80 and 100 effective to bind to any human immunodeficiency virus present in the subject, so as to thereby prevent the subject's CD4+ cells from becoming infected with human immunodeficiency virus.

113. A method of treating a subject having CD4+ cells infected with human immunodeficiency virus which comprises administering to the subject an amount of the formulation of any one of claims 1, 29, 42, 59, 80 and 100 effective to bind to any human immunodeficiency virus present in the subject, so as to thereby treat the subject having CD4+ cells infected with human immunodeficiency virus.

114. A method of making a pharmaceutical formulation comprising a CD4-IgG2 chimeric heterotetramer, which method comprises concentrating the heterotetramer from a source in the presence of a histidine buffer at a pH of between about 5.5 and 6.5 to produce a formulation having a concentration of said heterotetramer greater than about 15 mg/ml.

115. The method according to claim 114, wherein the concentration of the chimeric heterotetramer in said formulation is between about 15-30 mg/ml.

116. The method according to claim 115, wherein the concentration of the chimeric heterotetramer in said formulation is about 25 mg/ml.

117. The method according to claim 114, wherein the concentration of the chimeric heterotetramer in said formulation is between about 100-162 mg/ml.

118. The method according to claim 117, wherein the concentration of the chimeric heterotetramer in said formulation is about 100 mg/ml.

119. The method according to claim 117, wherein the concentration of the chimeric heterotetramer in said formulation is between about 140-150 mg/ml.

120. The method according to claim 100, which further comprises adding to said formulation at least one of an amino acid stabilizing agent, a lyoprotectant, a nonionic detergent and at least one osmolality adjusting agent.

121. The method according to claim 120, wherein the amino acid stabilizing agent is selected from the group consisting of alanine, glycine, proline and glycylglycine and is admixed in said formulation at a concentration of between about 25-150 mM.

122. The method according to claim 120, wherein the lyoprotectant is sucrose or trehalose and is admixed in said formulation at a concentration of between about 1.5-3%.

123. The method according to claim 120, wherein the nonionic detergent comprises a polysorbate composition and is admixed in said formulation at a concentration of between about 0.02-0.05%.

124. The method according to claim 120, wherein the at least one osmolality adjusting agent is selected from the group consisting of maltose, trehalose and glycine and is admixed in said formulation at a concentration of between about 4-10%.

125. The method according to claim 120, wherein the at least one osmolality adjusting agent is added to said formulation at a concentration to provide an osmolality of about 216-320 mOsm/kg.

126. The method according to claim 120, wherein the at least one osmolality adjusting agent is added to said

formulation at a concentration to provide an osmolality of about 220-300 mOsm/kg.

127. The method according to claim 120, wherein the at least one osmolality adjusting agent is added to said formulation at a concentration to provide an osmolality of about 280 mOsm/kg.

128. The method according to claim 114, wherein the chimeric heterotetramer is concentrated by ultrafiltration.

129. The method according to claim 128, wherein the ultrafiltration is performed by tangential flow filtration.

130. The method according to claim 128, wherein the ultrafiltration is performed by centrifugal filtration.

131. The method according to claim 128, wherein the ultrafiltration is performed by stirred cell filtration.

132. The method according to claim 114, further comprising lyophilization of the formulation.

133. An article of manufacture comprising:

(a) first packaging material containing a lyophilized pharmaceutical formulation according to any one of claims 1, 29, 42, 59, 80 and 100; and

(b) instructions for reconstituting the lyophilized formulation with a diluent to produce a CD4-IgG2 chimeric heterotetramer concentration in the reconstituted formulation of between about 15-162 mg/ml.

134. The article of manufacture of claim 133, further comprising a second packaging material containing a diluent.

135. The article of manufacture of claim 134, wherein the diluent is water-for-injection or physiological saline.

136. An article of manufacture comprising a packaging material containing therein a pharmaceutical formulation containing a CD4-IgG2 chimeric heterotetramer according to any one of claims 1, 29, 42, 59, 80 and 100 and a label providing instructions for using said formulation

in preventing infection of a subject by human immunodeficiency virus.

137. An article of manufacture comprising a packaging material containing therein a pharmaceutical formulation containing a CD4-IgG2 chimeric heterotetramer according to any one of claims 1, 29, 42, 59, 80 and 100 and a label providing instructions for using said formulation in treating subjects infected with human immunodeficiency virus.

138. A kit comprising a lyophilized pharmaceutical formulation according to any one of claims 1, 29, 42, 59, 80 and 100 and a diluent for reconstituting the lyophilized formulation.

139. The kit according to claim 138, wherein the diluent is water-for-injection or physiological saline.

140. The kit according to claim 138, further including instructions for use.

141. A kit comprising a pharmaceutical formulation according to any one of claims 1, 29, 42, 59, 80 and 100 and instructions for use.